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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DAVIS, RUTH A	

ART UNIT	PAPER NUMBER
1651	

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18

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/054,710	MASUDA ET AL.	
	Examiner	Art Unit	
	Ruth A. Davis	1651	

-- Th MAILING DATE of this communication app ars on th cover sheet with the correspondence address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *15,16,31 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,17-30,33-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed August 8, 2003 has been received and entered into the case. Claims 15, 16, 31 and 32 are withdrawn from consideration as being drawn to a non elected invention. Claims 1 – 14, 17 – 30 and 33 – 35 have been considered on the merits. All arguments have been fully considered.

The reference submitted on August 8, 2003 (Klagsburn) is acknowledged and has been considered.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1 – 14, 17 – 30 and 33 – 35 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 17 and their dependents remain vague and indefinite because the claims fail to recite what "effects" are being determined thereby not positively pointing out what constitutes an effect that has been determined. It is reiterated that the claims fail to define any limitation wherein a particular result (or lack thereof) indicates an "effect". Moreover, it remains unclear what effect, if any, must occur to practice the claimed invention.

Claims 1, 17 and their dependents remain confusing for reciting both "tissue engineered cartilage matrix" and "engineered cartilage tissue" because it is unclear if applicant is using the term interchangeably. For example, is the engineered cartilage tissue cultured in step (A) the same product as the tissue engineered cartilage matrix that is being observed for effects in the claimed method? Moreover, the claims stand indefinite because it is unclear if there are two (2) separate products or one (1).

Claims 1, 17 and their dependents remain indefinite because while the method is drawn to determining effects on an engineered cartilage tissue (ECT), step (B) allows for the determining step to occur on isolated chondrogenic cells before they have formed into the ECT. It is unclear how one could determine the effects of an agent on an ECT by contacting cells that have yet to form an ECT. Specifically, the claimed method requires determining effects of a test agent on a specified engineered cartilage product. It is unclear how contacting the test agent with intermediates and/or precursors of the end product are determining the effects of the agent on the cartilage product. Moreover, by practicing the claimed steps, one would not necessarily be determining effects of test agents on the engineered cartilage, but of cells only.

Claims 11 and 27 remain vague and indefinite because it is unclear if step (C) rather comprises enzymatically degrading the ECT, or further comprises enzymatically degrading ECT. Following the claimed method, it is unclear how culturing the product, contacting the product with a test agent, then enzymatically degrading the product, would determine effects of the test agent on the cartilage product. Moreover, it is unclear if enzymatically degrading the product after exposure to the test agent, achieves the claimed method of determining the effects of the test agent?

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1 – 8, 10, 14, 17 – 24, 26, 29 – 30 and 33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kai in view of Masuda.

Applicant claims a method for determining the effect of a test agent on a tissue engineered cartilage matrix, the method comprising culturing an engineered cartilage tissue (ECT), contacting test agents with cells or tissues of the ECT, and measuring the effect that the agents have on the ECT or cells thereof. The ECT is cultured by culturing isolated chondrogenic cells for a time sufficient to form a chondrogenic cell-associated matrix, and culturing the cells

with the cell-associated matrix on a semipermeable membrane in the presence of a growth factor for a time sufficient to form an ECT. The cells or tissues are selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix before or after culturing, and the ECT. Alternatively, the cells are selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix before or after culturing, and the ECT in the presence of a known modulator of cartilage tissue. The chondrogenic cell-associated matrix comprises aggrecan, collagen types II, IX, XI, matrix proteins, and hyaluronan and the ECT comprises collagens II, IX, XI, hyaluronan, and at least about 5 mg/cc3 aggrecan, the ratio of aggrecan : hyaluronan is about 10:1 – 200:1, and the ration of aggrecan : collagen is about 1:1 – 10:1. The isolated chondrogenic cells are isolated from articular cartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoids or cricoid cartilages, specifically fibrocartilage from ligament, tendon, meniscus, or intervertebral disc. The chondrogenic cells are cultured on an alginate medium, the measuring is performed without addition of extrinsic radioactivity and the method further comprises identifying one or more test agents that have desirable characteristics and producing the agents as a therapeutic drug. The modulator of the ECT tissue is a matrix stimulating agent, cytokine or TNF-alpha wherein the cytokine is interleukin 1 (IL-1).

Kai teaches a method for determining effects of agents on cartilage, wherein the cartilage is cultured with IL-1 or TNF, is contacted with the test agent, and is measured for effects of the test agent (abstract). The method is used to screen for therapeutic agents (abstract).

Kai does not teach the method wherein the cartilage is cultured in the manner claimed. However, Masuda teaches methods for culturing an engineered cartilage tissue, wherein isolated

chondrocytes are cultured in alginate for a time to allow a cell associated matrix to form (col.4 line 30-35). The cell associated matrix has at least about 5 mg/cc3 aggrecan, a ratio of aggrecan to hyaluronan of 10:1 to 200:1, and a ratio of aggrecan to collagen of about 1:1 to 10: (col.4 line 35-40). The chondrogenic cells are cultured on a semi-permeable membrane in the presence of growth factors (col. 4 line 44-46). The chondrocytes may be isolated from articular cartilage, fibrocartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoid or cricoid cartilages (col.5 line 31-38) and the resulting matrix comprises aggrecan, collagn II, IX, XI and hyaluronan (col.6 line 61-64). At the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to culture the cartilage of Kai using the methods of Masuda because it was a known method for culturing cartilage tissues. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by common culture practices in the art to culture the cartilage of Kai via the methods of Masuda with a reasonable expectation for successfully determining the effects of test agents on cartilage cultures. Although Masuda does not teach the fibrocartilage is from a ligament, tendon, meniscus or intervertebral discs, they were each well known sources of fibrocartilage. Moreover at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to use any of the above sources as the source of fibrocartilage in the methods of Masuda.

Applicant argues that there is no motivation to combine the references, that Kai does not teach culture conditions, that Kai and Masuda do not share similar culture conditions, and that examiner is using improper hindsight.

However, these arguments fail to persuade because the claims are drawn to a method for determining effects of test agents on a product, not a method of culturing cells. Kai specifically teaches a method wherein a test substance is contacted with cartilage cells and determining the effects of those test agents on the cells/cartilage. Furthermore, Masuda is evidence that the claimed limitations drawn to culturing techniques were well known and practiced in the art at the time the claimed invention was made. At the time of the claimed invention, one of ordinary skill in the art would certainly have been motivated to culture the cartilage cells of Masuda with a reasonable expectation for successfully obtaining engineered cartilage tissue useful in the method of Kai.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

6. Claims 1 – 10, 14, 17 – 26, 33 and 35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Purchio in view of Masuda.

Applicant claims a method for determining the effect of a test agent on a tissue engineered cartilage matrix, the method comprising culturing an engineered cartilage tissue

(ECT), contacting test agents with cells or tissues of the ECT, and measuring the effect that the agents have on the ECT or cells thereof. The ECT is cultured by culturing isolated chondrogenic cells for a time sufficient to form a chondrogenic cell-associated matrix, and culturing the cells with the cell-associated matrix on a semipermeable membrane in the presence of a growth factor for a time sufficient to form an ECT. The cells or tissues are selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix before or after culturing, and the ECT. Alternatively, the cells are selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix before or after culturing, and the ECT in the presence of a known modulator of cartilage tissue. The chondrogenic cell-associated matrix comprises aggrecan, collagen types II, IX, XI, matrix proteins, and hyaluronan and the ECT comprises collagens II, IX, XI, hyaluronan, and at least about 5 mg/cc3 aggrecan, the ratio of aggrecan : hyaluronan is about 10:1 – 200:1, and the ration of aggrecan : collagen is about 1:1 – 10:1. The isolated chondrogenic cells are isolated from articular cartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoids or cricoid cartilages, specifically fibrocartilage from ligament, tendon, meniscus, or intervertebral disc. The chondrogenic cells are cultured on an alginate medium, the measuring comprises measuring the amount of proteoglycan in the ECT, is performed without addition of extrinsic radioactivity and the method further comprises identifying one or more test agents that have desirable characteristics and producing the agents as a therapeutic drug. The culturing of ECT and the contacting the cells with the test agent occurs in the same well of a multi-well plate.

Purchio teaches methods for screening effects of test agents on cartilage cultures wherein the cultures are exposed to the test agents and the effects are measured (col.16 line 12-22).

Examples of such effects include the amount of proteoglycan (col.16 line 27-34). Specifically, chondrocytes are harvested from articular cartilage and cultured in multi-well plates (col.21 lines 18-60) and the test agents are identified for therapeutic and/or pharmaceutical compounds (col. 16). Purchio teaches that the chondrocytes can be isolated from articular or costal cartilage (col.11 line 62-65).

Purchio does not teach the method wherein the cartilage is cultured in the manner claimed. However, Masuda teaches methods for culturing an engineered cartilage tissue, wherein isolated chondrocytes are cultured in alginate for a time to allow a cell associated matrix to form (col.4 line 30-35). The cell associated matrix has at least about 5 mg/cc3 aggrecan, a ratio of aggrecan to hyaluronan of 10:1 to 200:1, and a ratio of aggrecan to collagen of about 1:1 to 10: (col.4 line 35-40). The chondrogenic cells are cultured on a semi-permeable membrane in the presence of growth factors (col. 4 line 44-46). The chondrocytes may be isolated from articular cartilage, fibrocartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoid or cricoid cartilages (col.5 line 31-38) and the resulting matrix comprises aggrecan, collagn II, IX, XI and hyaluronan (col.6 line 61-64). At the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to culture the cartilage of Purchio using the methods of Masuda because it was a known method for culturing cartilage tissues. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by common culture practices in the art to culture the cartilage of Purchio via the methods of Masuda with a reasonable expectation for successfully determining the effects of test agents on cartilage cultures. Although Masuda does not teach the fibrocartilage is from a ligament, tendon, meniscus or intervertebral discs, they were each well known sources of fibrocartilage. Moreover

at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to use any of the above sources as the source of fibrocartilage in the methods of Masuda.

Applicant argues that there is no motivation to combine the references, that Masuda is not a common practice, and that the references do not share similar culture conditions.

However, these arguments fail to persuade because the claims are drawn to a method for determining effects of test agents on a product, not a method of culturing cells. Purchio clearly teaches methods wherein a test substance is contacted with cartilage cells followed by a determination of the effects of those test agents on the cells/cartilage (col.16). Furthermore, the disclosure of Masuda is clear evidence that the limitations drawn to culturing techniques were well known and practiced in the art at the time the claimed invention was made. At the time of the claimed invention, one of ordinary skill in the art would certainly have been motivated to practice the determining methods of Purchio with the cartilage cells of Masuda with a reasonable expectation for successfully obtaining engineered cartilage tissue useful in the disclosed method of Purchio.

7. Claims 1 – 8, 17 – 24, 29 – 30 and 35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Saito in view of Masuda.

Applicant claims a method for determining the effect of a test agent on a tissue engineered cartilage matrix, the method comprising culturing an engineered cartilage tissue

(ECT), contacting test agents with cells or tissues of the ECT, and measuring the effect that the agents have on the ECT or cells thereof. The ECT is cultured by culturing isolated chondrogenic cells for a time sufficient to form a chondrogenic cell-associated matrix, and culturing the cells with the cell-associated matrix on a semipermeable membrane in the presence of a growth factor for a time sufficient to form an ECT. The cells or tissues are selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix before or after culturing, and the ECT. Alternatively, the cells are selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix before or after culturing, and the ECT in the presence of a known modulator of cartilage tissue. The chondrogenic cell-associated matrix comprises aggrecan, collagen types II, IX, XI, matrix proteins, and hyaluronan and the ECT comprises collagens II, IX, XI, hyaluronan, and at least about 5 mg/cc3 aggrecan, the ratio of aggrecan : hyaluronan is about 10:1 – 200:1, and the ration of aggrecan : collagen is about 1:1 – 10:1. The isolated chondrogenic cells are isolated from articular cartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoids or cricoid cartilages, specifically fibrocartilage from ligament, tendon, meniscus, or intervertebral disc. The chondrogenic cells are cultured on an alginate medium. The modulator of the ECT tissue is a matrix stimulating agent, cytokine or TNF-alpha wherein the cytokine is interleukin 1 (IL-1). Finally, the culturing and contacting step occur in the same well of a multi well plate.

Saito teaches culturing cartilage in multi well plates in the presences of IL-1 alpha, wherein the effects of the test agent were measured (p.727).

Saito does not teach the method wherein the cartilage is cultured in the manner claimed. However, Masuda teaches methods for culturing an engineered cartilage tissue, wherein isolated

chondrocytes are cultured in alginate for a time to allow a cell associated matrix to form (col.4 line 30-35). The cell associated matrix has at least about 5 mg/cc3 aggrecan, a ratio of aggrecan to hyaluronan of 10:1 to 200:1, and a ratio of aggrecan to collagen of about 1:1 to 10: (col.4 line 35-40). The chondrogenic cells are cultured on a semi-permeable membrane in the presence of growth factors (col. 4 line 44-46). The chondrocytes may be isolated from articular cartilage, fibrocartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoid or cricoid cartilages (col.5 line 31-38) and the resulting matrix comprises aggrecan, collagn II, IX, XI and hyaluronan (col.6 line 61-64). At the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to culture the cartilage of Saito using the methods of Masuda because it was a known method for culturing cartilage tissues. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by common culture practices in the art to culture the cartilage of Saito via the methods of Masuda with a reasonable expectation for successfully determining the effects of test agents on cartilage cultures. Although Masuda does not teach the fibrocartilage is from a ligament, tendon, meniscus or intervertebral discs, they were each well known sources of fibrocartilage. Moreover at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to use any of the above sources as the source of fibrocartilage in the methods of Masuda.

Applicant argues that there is no motivation to combine the references, that Saito uses explants and Masuda uses engineered cartilage tissue and therefore cannot be combined.

However, these arguments fail to persuade because the claims are drawn to a method for determining effects of test agents on a product, not a method of culturing cells. Saito clearly

teaches methods wherein a test substance is contacted with cartilage cells followed by a determination of the effects of those test agents on the cells/cartilage. While Saito does not teach cultured cartilage in the method, it would have been obvious to one of ordinary skill in the art to culture the cartilage tissue, since such methods were commonly known and practiced in the art at the time the claimed invention was made. Specifically, the disclosure of Masuda is clear evidence that the limitations drawn to culturing techniques were well known and practiced in the art at the time the claimed invention was made. Moreover, at the time of the claimed invention, one of ordinary skill in the art would certainly have been motivated to practice the determination methods of Saito with the cartilage cells of Masuda with a reasonable expectation for successfully obtaining engineered cartilage tissue useful in the disclosed method of Saito.

8. Claims 1 – 11, 17 – 27 and 29 – 30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Huch in view of Masuda.

Applicant claims a method for determining the effect of a test agent on a tissue engineered cartilage matrix, the method comprising culturing an engineered cartilage tissue (ECT), contacting test agents with cells or tissues of the ECT, and measuring the effect that the agents have on the ECT or cells thereof. The ECT is cultured by culturing isolated chondrogenic cells for a time sufficient to form a chondrogenic cell-associated matrix, and culturing the cells with the cell-associated matrix on a semipermeable membrane in the presence of a growth factor for a time sufficient to form an ECT. The cells or tissues are selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix

before or after culturing, and the ECT. Alternatively, the cells are selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix before or after culturing, and the ECT in the presence of a known modulator of cartilage tissue. The chondrogenic cell-associated matrix comprises aggrecan, collagen types II, IX, XI, matrix proteins, and hyaluronan and the ECT comprises collagens II, IX, XI, hyaluronan, and at least about 5 mg/cc3 aggrecan, the ratio of aggrecan : hyaluronan is about 10:1 – 200:1, and the ration of aggrecan : collagen is about 1:1 – 10:1. The isolated chondrogenic cells are isolated from articular cartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoids or cricoid cartilages, specifically fibrocartilage from ligament, tendon, meniscus, or intervertebral disc. The chondrogenic cells are cultured on an alginate medium, the measuring comprises measuring the amount of proteoglycan in the ECT, enzymatically degrading the ECT and is performed without addition of extrinsic radioactivity. The method further comprises identifying one or more test agents that have desirable characteristics and producing the agents as a therapeutic drug. The culturing of ECT and the contacting the cells with the test agent occurs in the same well of a multi-well plate. The modulator of the ECT tissue is a matrix stimulating agent, cytokine or TNF-alpha wherein the cytokine is interleukin 1.

Huch teaches methods for culturing articular chondrocytes in an alginate medium in the presence of a test agent, IL-1, wherein proteoglycan was measured (abstract). Specifically, the cartilage was degraded with enzymes, the chondrocytes were cultured with alginate in a multi-well plate in the presence of IL-1, and the amount of proteoglycan was measured (p. 2158).

Huch does not teach the method wherein the cartilage is cultured in the manner claimed. However, Masuda teaches methods for culturing an engineered cartilage tissue, wherein isolated

chondrocytes are cultured in alginate for a time to allow a cell associated matrix to form (col.4 line 30-35). The cell associated matrix has at least about 5 mg/cc3 aggrecan, a ratio of aggrecan to hyaluronan of 10:1 to 200:1, and a ratio of aggrecan to collagen of about 1:1 to 10: (col.4 line 35-40). The chondrogenic cells are cultured on a semi-permeable membrane in the presence of growth factors (col. 4 line 44-46). The chondrocytes may be isolated from articular cartilage, fibrocartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoid or cricoid cartilages (col.5 line 31-38) and the resulting matrix comprises aggrecan, collagn II, IX, XI and hyaluronan (col.6 line 61-64). At the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to culture the cartilage of Huch using the methods of Masuda because it was a known method for culturing cartilage tissues. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by common culture practices in the art to culture the cartilage of Huch via the methods of Masuda with a reasonable expectation for successfully determining the effects of test agents on cartilage cultures. Although Masuda does not teach the fibrocartilage is from a ligament, tendon, meniscus or intervertebral discs, they were each well known sources of fibrocartilage. Moreover at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to use any of the above sources as the source of fibrocartilage in the methods of Masuda.

Applicant argues that there is no motivation to combine the references, that Huch tests individual cells, that Masuda uses engineered cartilage tissue and therefore cannot be combined.

However, these arguments fail to persuade because the claims are drawn to a method for determining effects of test agents on a product, not a method of culturing cells. Huch clearly

teaches methods wherein a test substance is contacted with cartilage cells followed by a determination of the effects of those test agents on the cells/cartilage. Although Huch does not specifically teach cartilage tissue, cells of cartilage are specifically disclosed (also claimed in step B). Furthermore, Masuda is evidence that the claimed limitations drawn to culturing techniques were well known and practiced in the art at the time the claimed invention was made. At the time of the claimed invention, one of ordinary skill in the art would certainly have been motivated to culture the cartilage cells of Masuda with a reasonable expectation for successfully obtaining cartilage cells useful in the method of Huch.

9. Claims 1 – 8, 10, 14, 17 – 24, 26 and 33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lansbury in view of Masuda.

Applicant claims a method for determining the effect of a test agent on a tissue engineered cartilage matrix, the method comprising culturing an engineered cartilage tissue (ECT), contacting test agents with cells or tissues of the ECT, and measuring the effect that the agents have on the ECT or cells thereof. The ECT is cultured by culturing isolated chondrogenic cells for a time sufficient to form a chondrogenic cell-associated matrix, and culturing the cells with the cell-associated matrix on a semipermeable membrane in the presence of a growth factor for a time sufficient to form an ECT. The cells or tissues are selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix before or after culturing, and the ECT. Alternatively, the cells are selected from isolated chondrogenic cells, the chondrogenic cells during culture, the cells and cell-associated matrix

before or after culturing, and the ECT in the presence of a known modulator of cartilage tissue. The chondrogenic cell-associated matrix comprises aggrecan, collagen types II, IX, XI, matrix proteins, and hyaluronan and the ECT comprises collagens II, IX, XI, hyaluronan, and at least about 5 mg/cc3 aggrecan, the ratio of aggrecan : hyaluronan is about 10:1 – 200:1, and the ration of aggrecan : collagen is about 1:1 – 10:1. The isolated chondrogenic cells are isolated from articular cartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoids or cricoid cartilages, specifically fibrocartilage from ligament, tendon, meniscus, or intervertebral disc. The chondrogenic cells are cultured on an alginate medium, the measuring is performed without addition of extrinsic radioactivity and the method further comprises identifying one or more test agents that have desirable characteristics and producing the agents as a therapeutic drug.

Lansbury teaches methods for screening the effects of agents on cartilage cultures wherein a chondrocyte cell culture is incubated (or contacted) with the test agent and the effects are measured (claim 34). The method is used to identify agents with desirable, therapeutic characteristics, specifically the ability to repair damaged cartilage (claim 34).

Lansbury does not teach the method wherein the cartilage is cultured in the manner claimed. However, Masuda teaches methods for culturing an engineered cartilage tissue, wherein isolated chondrocytes are cultured in alginate for a time to allow a cell associated matrix to form (col.4 line 30-35). The cell associated matrix has at least about 5 mg/cc3 aggrecan, a ratio of aggrecan to hyaluronan of 10:1 to 200:1, and a ratio of aggrecan to collagen of about 1:1 to 10: (col.4 line 35-40). The chondrogenic cells are cultured on a semi-permeable membrane in the presence of growth factors (col. 4 line 44-46). The chondrocytes may be isolated from articular cartilage, fibrocartilage, costal, nasal, auricular, tracheal, epiglottic, thyroid, arytenoid

or cricoid cartilages (col.5 line 31-38) and the resulting matrix comprises aggrecan, collagn II, IX, XI and hyaluronan (col.6 line 61-64). At the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to culture the cartilage of Lansbury using the methods of Masuda because it was a known method for culturing cartilage tissues. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by common culture practices in the art to culture the cartilage of Lansbury via the methods of Masuda with a reasonable expectation for successfully determining the effects of test agents on cartilage cultures. Although Masuda does not teach the fibrocartilage is from a ligament, tendon, meniscus or intervertebral discs, they were each well known sources of fibrocartilage. Moreover at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to use any of the above sources as the source of fibrocartilage in the methods of Masuda.

Applicant argues that there is no motivation to combine the references, that Lansbury tests individual cells, that Masuda uses engineered cartilage tissue and therefore cannot be combined.

However, these arguments fail to persuade because the claims are drawn to a method for determining effects of test agents on a product, not a method of culturing cells. Lansbury clearly teaches methods wherein a test substance is contacted with cartilage cells followed by a determination of the effects of those test agents on the cells/cartilage. Although Lansbury does not specifically teach cartilage tissue, cells of cartilage are specifically disclosed (also claimed in step B). Furthermore, Masuda is evidence that the claimed limitations drawn to culturing

techniques were well known and practiced in the art at the time the claimed invention was made. At the time of the claimed invention, one of ordinary skill in the art would certainly have been motivated to culture the cartilage cells of Masuda with a reasonable expectation for successfully obtaining cartilage cells useful in the method of Lansbury.

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruth A. Davis whose telephone number is 703-308-6310. The examiner can normally be reached on M-H (7:00-4:30); altn. F (7:00-3:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 703-308-0196. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ruth A. Davis; rad
October 16, 2003.

LEON B. LANKFORD, JR.
PRIMARY EXAMINER